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10/524,021	02/09/2005	Yoshiji Yamada	050070	3971

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EXAMINER	
GREENE, JAIME M	

ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/524,021	YAMADA ET AL.	
	Examiner	Art Unit	
	JAIME M. GREENE	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-20* is/are pending in the application.

4a) Of the above claim(s) *2-4 and 6-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to papers filed 11/7/07. Claims 2-20 are pending, claims 2-4 and 6-16 have been previously withdrawn, claims 17-19 are new claims that have been withdrawn, and claims 5 and 20 are under examination on the merits. This action is FINAL.

Election/Restrictions

2. Applicant's election without traverse of Group I, claims 1 and 5, and polymorphisms 1, 3, and 4 in the reply filed on 7/12/07 is acknowledged. Claim 1 has been cancelled, and therefore, claim 5 and new claim 20 are under examination on the merits.

3. Claims 2-4, and 6-16 were previously withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. New claims 17-19 have also been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

4. Election was made **without** traverse in the reply filed on 7/12/07.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim 20 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Claim 20 recites a method of diagnosing risk of restenosis after coronary angioplasty in a Japanese man, however, step (i) requires analyzing polymorphisms in a human nucleic acid sample. It is unclear if the sample is from the Japanese man or from any human, and it is further unclear how one accomplishes said method if the sample is not from a Japanese man. Applicant is required to clarify.

Withdrawn Claim Rejections

8. Applicant's arguments filed 11/7/07, with respect to the 35 USC § 112 Written Description rejection have been fully considered and are persuasive. Therefore, in light of the cancellation of claim 1 and the amendment of claim 5 to include the term "human", the rejection has been withdrawn.

9. In light of the cancellation of claim 1, the 102 rejections of claim 1 have been withdrawn.

Claim Rejections - 35 USC § 112 Enablement

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5 and 20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for diagnosing the risk of restenosis after coronary angioplasty in a Japanese man, comprising:

(i) obtaining a nucleic acid sample from a Japanese man;

(ii) analyzing the following polymorphisms (1), (3) and (4) in the nucleic acid sample; (1) a T or C polymorphism at the base number position 3932 (the 3932nd base of SEQ ID NO:I) of the human apolipoprotein E gene ; (3) a C or A polymorphism at the base number position -863 (the 197th base of SEQ ID NO:3)of the human tumor necrosis factor-α gene; (4) a C or T polymorphism at the base number position 825 (the 831st base of SEQ ID NO:4)of the human G-protein 133 subunit gene;

(iii) determining, based on the information about polymorphism which was obtained in the step (i), the genotype of the nucleic acid sample; and

(iv) assessing a genetic risk or restenosis based on the genotype determined, wherein the presence of a (1) T or C polymorphism at the base number position 3932 (the 3932nd base of SEQ ID NO:1) of the human apolipoprotein E gene ; (3) a C or A polymorphism at the base number position -863 (the 197th base of SEQ ID NO:3)of the human tumor necrosis factor- α gene; and (4) a C or T polymorphism at the base number position 825 (the 831st base of SEQ ID NO:4)of the human G-protein 133 subunit gene indicates a genetic risk of restenosis after coronary angioplasty,

does not reasonably provide enablement for a method for diagnosing the risk of restenosis after coronary angioplasty in a human or Japanese man subject, comprising the following steps (i) to (iii): (i) analyzing the following polymorphisms (1), (3) and (4) in

a human nucleic acid sample; (1) polymorphism at the base number position 3932 (the 3932nd base of SEQ ID NO:I) of the human apolipoprotein E gene ; (3) polymorphism at the base number position -863 (the 197th base of SEQ ID NO:3)of the human tumor necrosis factor-c~ gene; (4) polymorphism at the base number position 825 (the 831st base of SEQ ID NO:4)of the human G-protein [33 subunit gene; (ii) determining, based on the information about polymorphism which was obtained in the step (i), the genotype of the nucleic acid sample; and (iii) assessing, based on the genotype determined, a genetic risk of restenosis after coronary angioplasty. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

These claims are not enabled for reasons of record which have been reiterated and are further described below as well as for reasons necessitated by amendment.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation (*United States v. Teletronics Inc*, 8 USPQ2d 1217 (Fed Cir. 1988)). Whether undue experimentation is needed is not based on a single factor, but rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986)) and *In re Wands* 8 USPQ2d 1400 (Fed. Cir. 1988)). These factors include the following:

The breadth of the claims and nature of the invention

Claim 5 is drawn to a method for diagnosing the risk of restenosis after coronary angioplasty in a human subject, comprising the following steps (i) to (iii): (i) analyzing

the followinq polymorphisms (1), (3) and (4) in a human nucleic acid sample; (1) polymorphism at the base number position 3932 (the 3932nd base of SEQ ID NO:l) of the human apolipoprotein E gene ; (3) polymorphism at the base number position -863 (the 197th base of SEQ ID NO:3)of the human tumor necrosis factor-c~ gene; (4) polymorphism at the base number position 825 (the 831st base of SEQ ID NO:4)of the human G-protein [33 subunit gene; (ii) determining, based on the information about polymorphism which was obtained in the step (i), the genotype of the nucleic acid sample; and (iii) assessing, based on the genotype determined, a genetic risk of restenosis after coronary angioplasty..

Claim 20 is drawn to method for diagnosing the risk of restenosis after coronary angioplasty in a Japanese man, comprising the following steps (i) to (iii): (i) analyzing the following polymorphisms (1), (3) and (4) in a human nucleic acid sample; (1) polymorphism at the base number position 3932 (the 3932nd base of SEQ ID NO:l) of the human apolipoprotein E gene ; (3) polymorphism at the base number position -863 (the 197th base of SEQ ID NO:3)of the human tumor necrosis factor-~ gene; (4) polymorphism at the base number position 825 (the 831st base of SEQ ID NO:4)of the human G-protein 133 subunit gene; (ii) determining, based on the information about polymorphism which was obtained in the step (i), the genotype of the nucleic acid sample; and (iii) assessing, based on the genotype determined, a genetic risk of restenosis after coronary angioplasty.

The nature of the invention not only involves determining the genotype of the elected polymorphisms but also correlating those genotypes with a risk for restenosis.

Guidance in the Specification and Working Examples

The specification teaches the sequences of the elected polymorphisms for the human genes and provides SEQ ID NOs 1, 3, and 4 to identify the human genes and polymorphisms in those genes.

The specification also describes (pages 58-65) a study in a population of Japanese 1313 men and 556 women that quantitates a correlation between specific gene sequences and restenosis in order to identify the risk of restenosis predicted by the presence of certain polymorphic sequences. With regard to the elected polymorphisms, the specification provides data that demonstrates an odds ratio of 7.33 as a predictor of risk of restenosis in Japanese men when the patient has a defined polymorphism in each gene. However, the specification does not provide information on how the odds ratio was determined. Specifically, although there are p-values regarding the correlation of each polymorphism with restenosis, the manner in which the applicants determined those p-values is not provided. For example, a significant p-value of 0.05 could indicate that the chance of a patient having one polymorphism and then restenosis is equal to or only slightly (51%) higher than the chance that the patient has the opposite polymorphism. Thereby, the odds ratio provides limited information regarding the risk of a patient developing restenosis when that patient has polymorphisms at the base number position 3932 of the apolipoprotein E gene; at the base number position -863 of the tumor necrosis factor-alpha gene; and at the base number position 825 of G-protein beta 3 subunit gene.

In women, polymorphisms at the base number position 3932 of the apolipoprotein E gene and at the base number position -863 of the tumor necrosis factor-alpha gene were examined relative to their role in correlating with a risk for restenosis, however the polymorphism at the base number position 825 of G-protein .beta.3 subunit gene was not examined for its role in restenosis in women. Also, there is no corresponding risk factor result in women for the combination of polymorphisms at the base number position 3932 of the apolipoprotein E gene; at the base number position -863 of the tumor necrosis factor-alpha gene; and at the base number position 825 of G-protein beta 3 subunit gene.

As previously stated, the nature of the invention not only involves determining the genotype of the elected polymorphisms but also correlating those genotypes with a risk for restenosis. However, the specification only analyzes the risk of restenosis when a Japanese man has the following nucleotides at the polymorphic site: (1) a T or C polymorphism at the base number position 3932 (the 3932nd base of SEQ ID NO:l) of the human apolipoprotein E gene ; (3) a C or A polymorphism at the base number position -863 (the 197th base of SEQ ID NO:3)of the human tumor necrosis factor-~ gene; (4) a C or T polymorphism at the base number position 825 (the 831st base of SEQ ID NO:4)of the human G-protein 133 subunit gene (Figure 12). Also, while the specification does provide an odds ratio for these polymorphisms, the specification does not provide the significance, CI, of each odds ratio determined for the combinations of polymorphisms.

The unpredictability of the art, the state of the prior art, level of skill in the art

While the state of the art and level of skill in the art with regard to detection of a gene expression levels is high, the level of unpredictability in associating any particular expression of a particular gene or combination of genes with a phenotype is even higher. The level of unpredictability is demonstrated by the prior art, the post filing art, and the instant specification.

The art teaches genetic variations and associations are often irreproducible. Hirschhorn et al. (Genetics in Medicine. Vol. 4, No. 2, pages 45-61, March 2002) teaches that most reported associations are not robust. Of the 166 associations studied three or more times, only 6 have been consistently replicated. Hirschhorn et al. suggest a number of reasons for the irreproducibility of studies, suggesting population stratification, linkage disequilibrium, gene-gene or gene-environment interactions, and weak genetic effects and lack of power are possible factors that lead to such irreproducibility. Hirschhorn et al. caution that the current irreproducibility of most association studies should raise a cautionary alarm when considering their use as diagnostics and prognostics (p. 60, Col. 2). Thus, Hirschhorn cautions in drawing conclusions from a single report of an association between a gene and a disease type (in this instance tumor detection).

Ioannidis (Nature Genetics, Vol. 29, pages 306-309, November 2001) teaches that the results of the first study correlate only modestly with subsequent research on the same association (abstract). Ioannidis teaches that both bias and genuine population diversity might explain why early association studies tend to overestimate the disease protection or predisposition conferred by a genetic polymorphism (abstract).

Therefore the size of a population studied will effect the correlation of a gene expression to tumor detection.

Additionally, post-filing art reveals that most gene association studies are typically wrong. Lucentini (The Scientist, 2004, 18(24):20) teaches that it is strikingly common for follow-up studies to find gene-disease associations wrong (left column, 3rd paragraph). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a disease there is only roughly a one-third chance that the study will reliably confirm the finding (left column, 3rd paragraph). Lucentini teaches that bigger sample sizes and more family-based studies, along with revising statistical methods, should be included in the gene association studies (middle column, 1st complete paragraph).

The specification only provides data from a single study, and the data is incomplete, in that it does not disclose the probability that a patient having the elected polymorphisms with any nucleotide at the polymorphic site will develop restenosis. Also, the study is limited to Japanese men, and does not include data from other human populations. Therefore, the information provided in the specification along with the prior and post filing art indicate that using any nucleotide at the polymorphic sites to determine risk of restenosis is unpredictable.

The quantity of experimentation

Given the lack of guidance in the specification with regard to any nucleotide at the elected polymorphic sites and restenosis, the lack of study in populations aside from Japanese men, and the assessment in the art of the difficulties associated with using

genes to predict susceptibility to complex disorders, and the lack of significance of the assess odds ratios, the quantity of experimentation required to reach the conclusion of risk for developing restenosis is large. The skilled artisan would have to perform an extremely large study that included different populations and familial studies in along with a large amount of trial and error analysis to determine if in fact there is a way to predictably correlate any nucleotide of the elected polymorphisms with risk of restenosis. Given the lack of guidance in the specification and the post filing art with respect to accurately testing for genetic correlations with medical conditions, such analysis is replete with unpredictable experimentation and is considered undue.

Response to Arguments

10. Applicants arguments filed 11/7/07 have been fully considered and are partially persuasive.

11. Applicants argue that the examples teach how the polymorphisms are associated with restenosis. This has been found partially persuasive, and as such, the rejection is now a scope of enablement, and the enabled scope has been indicated.

12. Applicant argues that information in the specification describes the evaluation of odds ratio. This argument has been considered and has been found persuasive. Therefore, arguments pertaining to the calculation of odds ratio have been removed from the rejection.

13. Applicants argue that the specification does provide data for diagnosing risk of restenosis in women and Applicants point to paragraphs 172 and 354 as evidence. This is not found persuasive, as neither paragraph demonstrates the use of the

combination of polymorphisms in data collected from women as predictive of restenosis. Also, while paragraph 354 points to literature describing a correlation between one of the polymorphisms and restenosis, the literature does not study the combination, which is the claimed invention in this application, and therefore the literature describing the single association does not enable the combination in the claimed invention. Further, figures 14-16, which is data from the women studied, provide no data demonstrating that the combination of the 3 elected polymorphisms can be used to predict risk of restenosis in women.

Conclusion

2. None of the claims have been allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAIME M. GREENE whose telephone number is (571)270-3052. The examiner can normally be reached on Monday-Thursday, 7:30am-5:00pm, ALT. Friday, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jaime M. Greene 2/15/08

/Ram R. Shukla/
Supervisory Patent Examiner, Art Unit 1634